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EXAMINER	
KIM, ALEXANDER D	

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1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,662	RATCLIFFE ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-25,27-29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) *7-25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *HIF-1 Human polypeptide*.

DETAILED ACTION

Application Status

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/06/2008 has been entered.

Applicants' amendment canceling Claims 2-3, 26 and 30; amending Claims 1, 4-6, 29 and 33 in the paper of 10/06/2008 is acknowledged. Claims 1, 4-25, 27-29 and 31-33 are pending in the instant office action. Claims 7-25, 27-28 are withdrawn as being drawn to non-elected invention. Claims 1, 4-6, 29 and 31-33 and will be examined herein.

Withdrawn-Compliance with Sequence Rules

2. The previous non-compliance with Sequence Rules for the Table 2 is withdrawn by virtue of Applicants' argument (i.e., the description of Table 2 filed by the Applicants (see page 3, filed on 12/19/2007) recites "Table 2, Partial sequence alignment of FIH with a selection of JmjC domain containing protein (SEQ ID NOs 4-20, respectively, in order of appearance)" has 17 polypeptides).

3. The previous non-compliance with Sequence Rules for the polypeptide in page 35, line 16, for not reciting appropriate SEQ ID NO, is withdrawn by virtue of Applicants' argument (i.e., the previous specification amendment filed on 12/29/2007 recites "SEQ ID NO: 3).

Withdrawn-Objections to the Specification

4. The previous objection to the specification, because the Table 2 has many gray areas wherein amino acid(s) cannot be deciphered, is withdrawn by virtue of newly filed Table 2 in the specification amendment filed on 10/06/2008, page 2.

Objections to the Specification

5. The specification is objected to because of the following informalities:

The amendment to the specification filed 10/06/2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

(a) Applicants have changed the recitation of "(4)" in the sequence of Ce Q9HI67 (i.e., 6th polypeptide, see original specification on page 42) into "(0)". Applicants have changed the recitation of "(16)" and "(1)" in the sequence of Dm Q9VHH9 (i.e., 7th polypeptide, see original specification on page 42) into "(17)" and "(0)", respectively.

(b) The SEQ ID NO: 5-25 filed on 12/19/2007 are not supported by the original SEQ ID NOs: 5-25, filed on 4/15/2005, respectively. The Applicants have made changes in the polypeptide identified by specific SEQ ID NOs; wherein the changes in the listing may be addition of new sequence(s), deletion of original sequence(s), and shuffling the polypeptide placing under different SEQ ID NO(s). For example, originally filed SEQ ID NO: 21 is apparently now SEQ ID NO: 30 which is confusing at best. The polypeptide identified by a specific SEQ ID NO should keep the original SEQ ID NO; add any new polypeptide under new SEQ ID NO; and provide support of the newly filed polypeptide sequence(s). For example, the newly filed polypeptide having 62 amino acids (i.e., identified as SEQ ID NO: 5) is not supported by original Sequence Listing because there is no polypeptide with 62 amino acids. The polypeptide identified as SEQ ID NO: 30 is now has SEQ ID NO: 21 in the newly filed sequence listing.

(c) The SEQ ID NOs: 5-11 in the newly filed Sequence Listing on 12/19/2007 contain many Xaa, which are not supported by the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action and/or appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 112

6. The previous rejection of Claims 6 and 33 are rejected under of 35 U.S.C. 112, second paragraph, for reciting the "Asn 803" without the point of reference for the

position 803 is withdrawn by virtue of Applicants' amendment (i.e., deleting the term Asn 803).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 4-6, 29 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1 (Claims 4-6 dependent therefrom) and 29 (Claims 31-33 dependent therefrom) are drawn to a method of identifying, screening, characterizing or designing a chemical entity comprising a structural model of said FIH with a structural model of chemical entity in silico without any testing step in vitro or in vivo using an identified chemical(s); wherein the activity of polypeptide can not be measured in silico. Thus, the scope of recited term "retains asparaginyl hydroxylase activity" is indefinite and wholly unclear how the activity can be determined without an active step of measuring it wherein the instant claims encompass a method having a step of in silico simulation involving structural model only. Thus, for the examination purpose, the claims reciting "retains asparaginyl hydroxylase activity" has been interpreted as having no patentable weight for the claimed method.

(b) Claims 1 (Claims 4-6 dependent therefrom) and 29 (Claims 31-33 dependent therefrom) recite the term "mimics" in many places, for example, "a chemical entity which mimics or binds to a FIH". It is wholly unclear how a chemical entity identified by the claimed methods would mimics a FIH polypeptide.

(c) Claims 1 (Claims 4-6 dependent therefrom) and 29 (Claims 31-33 dependent therefrom) recite "the structural factors or structural coordinates shown in Table 3". It is clear that the Table 3 is the structural coordinates; however, it is unclear the scope of recited "the structural factors". Is the factors includes a space group, unit cell dimensions, and/or any primary structure of amino acid sequence?

(d) Claims 6 and 33 recites "said asparagine residue" which should be in the SEQ ID NO: 24 or 25. Polypeptide of SEQ ID NO: 24 has Asn, however, the polypeptide of SEQ ID NO: 25 does not have Asn(N); thus, the scope of claimed limitation is unclear which Asn is the "said asparagine residue" in Claims 6 and 33.

(e) Claim 29 (Claims 31-33 dependent therefrom) recites the method step of "using the structural coordinates shown in Table 3". Claim 29 is indefinite because it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

(f) Claims 1, 4-6, 29 and 31-33 are deemed indefinite because they recite that the method step of identifying an entity that binds to HIF can be used by using the "*structure factors* or structure coordinates of Table 3". However, it is noted that

"structure factors" are merely a mathematical description of how the crystal scatters incident radiation and thus *cannot* be used in the method as stated.

(f) Claims 1 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those involving any sort of identifying step. The methods are performed *in silico* and merely "comparing structures" between HIF and a chemical entity does not mean that any sort of identification step has occurred (e.g. identifying those chemical entities that fit in the binding pocket, etc.).

Appropriate correction and or clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

8. Claims 1, 4-6, 29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, **new matter**, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(a) Claims 1 (Claims 4-6 dependent therefrom) and 29 (Claims 31-33 dependent therefrom) recite "wherein the fragment or mutant retains asparaginyl hydroxylase activity" which is not supported by the original disclosure.

(b) Claims 6 and 33 recites "SEQ ID NO: 24 or 25 or a fragment thereof or a variant having at least 90% identity" (which are polypeptide having 12 amino acids or a fragment thereof or a variant having at least 90% identity), which are not supported by the original disclosure.

The applicant is advised to point out the support in the original disclosure or amend the instant claims.

9. Claims 1, 4-6, 29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 1, 3-6 and 29-33. In response to this rejection, applicants have cancelled Claims 2-3, 26 and 30; amended Claims 1, 4-6, 29 and 33; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the present amendment renders the instant rejection moot and requested this rejection be withdrawn (see middle of page 15, Remarks filed on 10/6/2008).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Instant application describes a method step involved with four structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (e.g. these four separate structures are collectively referred to as "Table 3") for a method of identifying, screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor consisting SEQ ID NO: 21 and 22 (FIH, that is an inducible factor asparagine hydroxylase) identified as Q969Q7 (NCBI database). However, the breadth of Claim 1 (Claims 4-6 dependent therefrom) is drawn to a genus of methods that comprise comparing a structural model of said FIH (comprising SEQ ID NO: 21 or any fragment or any mutant thereof that adopts any similar 3-dimensional structure to a structure described in the coordinates in Table 3 wherein the fragment or mutant retains asparaginyl hydroxylase activity) "for said chemical entity" (which is not an active step because it is an intended use of comparing step); wherein the FIH structural model is derived from any "structural factors" or any structural coordinates (including any portion) from Table 3. Claim 29 (Claims 31-33 dependent therefrom) is also drawn to genus of methods comprising using, screening, characterizing or designing any chemical entity that mimics or binds to any FIH comprising SEQ ID NO: 21, any fragment or any mutant thereof described by the structural factors or structural coordinates of Table 3; wherein said FIH is very widely varying genus of FIH including, but not limited to, any protein or enzymes encompassed by any fragment or mutant of SEQ ID NO: 21; wherein the method step of using, identifying, screening, characterizing or designing is not limited to any parameter of said steps. For claims drawn to a genus, MPEP § 2163 states the

written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Instant application describes four structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (see Table 3) for a method of identifying, screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor (FIH, that is an inducible factor asparagine hydroxylase) identified as Q969Q7 (NCBI database). The claimed method of using a genus of FIH structure described above cannot be adequately described by the disclosure of species of the structure coordinates in the Table 3. The species of instant method or the prior art does not correlate structure and function from species to genus which have unlimited structural features of fragment or mutant of SEQ ID NO: 21. Prior art does not teach a correlation between a structure and function for very broadly claimed genus method. The specification and prior art do not provide adequately any method steps commonly possessed by members of the genus which distinguish the species

within the genus from other structural features of method step(s) such that one can visualize or recognize the identity of the members of the genus. Finally, the species which are described in the specification are not deemed to be representative of the broad and variable genus of structures used encompassed in the instant method claims. Thus, given the lack of description of a representative number of species in claimed method steps, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

10. Claims 1, 4-6, 29 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method step involved with four structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (see Table 3) for a method of identifying , screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor consisting SEQ ID NO: 21 and 22 (FIH, that is an inducible factor asparagine hydroxylase) identified as Q969Q7 (NCBI database); **does not** reasonably provide enablement for genus method comprises comparing a structural model of said FIH (comprising SEQ ID NO: 21 or any fragment or any mutant thereof that adopts any similar 3-dimensional structure to a structure described in the coordinates in Table 3 wherein the fragment or mutant retains asparaginyl hydroxylase activity) "for said chemical entity" (which is not an active step because it is an intended use of comparing step); wherein the FIH structural model is derived from any structural factors or any structural coordinates (including any portion)

from Table 3; and **does not** reasonably provide enablement for genus method comprising using, screening, characterizing or designing any chemical entity that mimics or binds to any FIH comprising SEQ ID NO: 21, any fragment or any mutant thereof described by the structural factors or structural coordinates of Table 3; wherein said FIH is very widely varying genus of FIH including, but not limited to, any protein or enzymes encompassed by any fragment or mutant of SEQ ID NO: 21; wherein the method step of using, identifying, screening, characterizing or designing is not limited to any parameter of said steps.

The rejection was stated in the previous office action as it applied to previous Claims 1, 3-6 and 29-33. In response to this rejection, applicants have cancelled Claims 2-3, 26 and 30; amended Claims 1, 4-6, 29 and 33; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the present amendment renders the instant rejection moot and requested this rejection be withdrawn (see bottom of page 15, Remarks filed on 10/6/2008). However, the breadth of Claim 1 (Claims 4-6 dependent therefrom) is drawn to a genus of method comprises comparing a structural model of said FIH (comprising SEQ ID NO: 21 or any fragment or any mutant thereof that adopts any similar 3-dimensional structure to a structure described in the coordinates in Table 3 wherein the fragment or mutant retains asparaginyl hydroxylase activity) "for said chemical entity" (which is not an active step because it is an intended use of comparing step); wherein the FIH structural model is derived from any structural factors or any structural coordinates (including any portion) from Table 3. Claim 29 (Claims 31-33

dependent therefrom) is drawn to genus a method comprising using, screening, characterizing or designing any chemical entity that mimics or binds to any FIH comprising SEQ ID NO: 21, any fragment or any mutant thereof described by the structural factors or structural coordinates of Table 3; wherein said FIH is very widely varying genus of FIH including, but not limited to, any protein or enzymes encompassed by any fragment or mutant of SEQ ID NO: 21; wherein the method step of using, identifying, screening, characterizing or designing is not limited to any parameter of said steps. The instant specification or the prior art do not describe very broadly claimed method for identifying, screening, characterizing or designing any chemical entity (including a polypeptide having 90% identity of SEQ ID NO: 24 or 25, fragment or variants thereof) that mimics or binds to any FIH (including any fragment and mutant of SEQ ID NO: 21) using any structural factors or any coordinates of Table 3. Applicants and prior art disclose no direction or guidance as to how make and use the full scope of claimed method as described by the breadth of claims above. It is unpredictable to make and use the claimed method for finding any chemical entity that mimics or binds to the genus of any FIH polypeptide encompassed by the claims. The said unpredictability makes the relative skill required in the art very high. For all of the above reason, it would require undue experimentation necessary for claimed method to identify, screen, characterize or design a chemical entity that mimics or binds to any FIH.

Claim Rejections - 35 USC § 102

11. Claims 1, 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hewitson et al. (May 31, 2002 E. publication, The Journal of Biological Chemistry, vol. 149, page 26351-26355).

The rejection was stated in the previous office action as it applied to previous Claims 1, 3, 5-6 and 29, 31-33. In response to this rejection, applicants have cancelled Claims 2-3, 26 and 30; amended Claims 1, 4-6, 29 and 33; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Hewitson does not disclose all of the elements of the instant claims as presently amended. In particular, any crystal structure obtained from the FIH of the instant claims or any structural coordinates obtained therefrom (see bottom of page 16, Remarks filed on 10/6/2008).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The method disclosed by Hewitson et al. meet all limitations of presently amended claims because the presently amended claims are broad enough to encompasses a method for identifying any chemical entity to FIH comprising SEQ ID NO: 21, any fragment or any mutant thereof. The structural coordinates are also met by the method of displaying the three-dimensional structure (which is produced by the coordinates for three dimensional structure) as shown in the Figure 2 on page 26354; wherein the claimed method is not limited to the coordinates of Table 3, but encompasses any structural factors or any structural coordinates (including any portion) of Table 3 which represents structure(s) of any polypeptide of fragment or

Comment [SMM1]: Alex in order to maintain this rejection you need to make another 112 2nd rejection because of because of the new limitation "which retains aparagyinly hydroxylase activity." You have rejected this under new matter but you cannot ignore the limitation. I would further reject these claims under 112 2nd based on this new limitation and say that *in silico* structures don't have ANY activity because they are virtual and thus it is essentially a non-limitation and this is how you are interpreting it. You then need to make this clear here in your 102 rejection why you are essentially ignoring the limitation.

AK: I was treating the limitation as the preamble (a long preamble and sometime the preamble do contribute to the step up to a certain extend) thus, having no patentable weight. But to make it clear I added 112 2nd above and added more explanation below. Is these corrections make better sense?

mutant of SEQ ID NO: 21, or any model thereof that adapts a similar 3-dimensional structure.

As previously disclosed, the recited FIH is not clearly defined by the instant specification, the instant FIH comprising a fragment or mutant of SEQ ID NO: 21, which encompass any "Factor Inhibiting HIF molecule", not limited to, enzymes belonging to the same family as the HIF hydroxylases, i.e. utilizing dioxygen (a cosubstrate), 2-oxoglutarate (2OG) (a cosubstrate) and Fe(II) (a cofactor). "Such enzymes are exemplified by phytanoyl coenzyme A hydroxylase, procollagen prolyl-r-hydroxylase, procollagen prolyl-3-hydroxylase, gamma-butyrobetaine hydroxylase, Alk B (a DNA repair enzyme) and other including predicted 2OG oxygenases identified on the basis of sequence analysis including a sub-family related to FIH (Hewitson et al. J BIOL CHEM 277 (29): 26351-26355, 2002)", according to the instant specification page 2, middle. Thus, the PMI or CAS1 shown in the sequence alignment of Figure 2-A (which includes instant FIH), see page 26354, by the Hewitson et al. is encompassed by a very broad FIH comprising fragment or mutant of SEQ ID NO: 21.

Hewitson et al. teach a method comprising comparing a structural model of phosphomannose isomerase (PMI) complexed with zinc, which is encompassed by the term FIH and a chemical entity, respectively, as shown in the three-dimensional structure in Figure 2-B, wherein the PMI three-dimensional structure meets the recited limitation of "structural model of said FIH is derived from structural factors or coordinates shown in Table 3" in Claim 1; wherein said FIH is any polypeptide comprising a fragment or a mutant of SEQ ID NO: 21; thus, meeting the limitation of

Claim 1 because as noted above in the 112 2nd paragraph rejection, the limitation regarding the activity requirement has been deemed indefinite because *in silico* structures have no activity by virtue of being virtual images. The binding of Zn in the protein crystal structure of Hewitson et al. meets the limitations of Claim 4. Also, in addition to the 35 U.S.C 112, 2nd rejection above regarding the term "retains asparaginyl hydroxylase activity", the "identifying, screening, characterizing or designing a chemical entity which mimics or binds to FIH polypeptide comprising SEQ ID NO: 21 or a fragment or mutant thereof ... wherein the fragment or mutant retains asparaginyl hydroxylase activity" is a preamble reciting an intended use, which does not contribute any limitations to the claimed method steps and given no patentable weight as an active method step. See *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir.1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation") and also MPEP 2111.02, Section II. The Hewitson et al. reference recites zinc(II) inhibits FIH (see middle of right column, page 26353) and in view of the assay using GST-HIF-1α-(775-826) as a substrate (see FIH Assays in bottom left column, page 26352), wherein the FIH of Hewitson et al. hydroxylate Asn803 of HIF (see title and bottom right column, page 26351); thus, the hydroxylation assay by Hewitson et al. using zinc meets the limitations of Claim 5. Thus, the method of Hewitson et al. anticipates Claims 1 and 4-5.

Claim Rejections - 35 USC § 103

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hewitson et al. (May 31, 2002 E. publication, The Journal of Biological Chemistry, vol. 149, page 26351-26355).

Hewitson et al. teach a method comprising comparing a structural model of phosphomannose isomerase (PMI) complexed with zinc, which are encompassed by the term FIH and a chemical entity, respectively, as shown in the three-dimensional structure in Figure 2-B, wherein the PMI three-dimensional structure meets the recited limitation of "structural model of said FIH is derived from structural factors or coordinates shown in Table 3" in Claim 1; wherein said FIH is any polypeptide comprising fragment or mutant of SEQ ID NO: 21; thus, meeting the limitation of Claim 1 because as noted above in the 112 2nd paragraph rejection, the limitation regarding the activity requirement has been deemed indefinite because *in silico* structures have no activity by virtue of being virtual images. The binding of Zn in the protein crystal structure of Hewitson et al. meets the limitations of Claim 4. Also addition to the 35 U.S.C 112, 2nd rejection above regarding the term "retains asparaginyl hydroxylase activity", the "identifying, screening, characterizing or designing a chemical entity which mimics or binds to FIH polypeptide comprising SEQ ID NO21 or a fragment or mutant thereof ... wherein the fragment or mutant retains asparaginyl hydroxylase activity" is a preamble reciting an intended use, which does not contribute any limitations to the claimed method steps and given no patentable weight as an active method step. The Hewitson et al. reference recites zinc(II) inhibits FIH (see middle of right column, page

26353) and in view of the assay using HIF-1α-(775-826) as a substrate (see FIH Assays in bottom left column, page 26352), wherein the FIH of Hewitson et al. hydroxylate Asn803 of HIF (see title and bottom right column, page 26351); thus, the hydroxylation assay by Hewitson et al. using zinc meets the limitations of Claim 5. Thus, the method of Hewitson et al. anticipates Claims **1 and 4-5**.

Hewitson et al. also teach the "Inclusion of N-oxaloylglycine in the FIH/HIF-1α CAD reaction step inhibited the effect of FIH" (see description of Figure 1, on page 26353) that is effecting the hydroxylation of Asn; wherein the HIF- 1α have polypeptide of 775-826 (i.e., DLACR LLGQSMDES LPQ LTSYDC EVNAPI QGSR NLLQGEELLR ALDQVN, see HIF-1 Human polypeptide in the attachment, the sequence identical to SEQ ID NO: 24 is underlined) ; which meets the limitation of **Claim 6** in part (i.e., contacting said chemical entity of a HIF polypeptide comprising a fragment of SEQ ID NO: 24) and retains the capacity to bind to FIH, fragment or mutant thereof as evidenced by the 100% identity.

Hewitson et al. do not teach a method of comparing N-oxaloylglycine with the three-dimensional structural model of Hewitson et al. described above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place three-dimensional structure of N-oxaloylglycine in the active site of protein structure shown in the Figure 2 B on page 26354) because the interaction of N-oxaloylglycine with the protein reveals active site residues or potential interaction that is more favorable; then identify the active site residue(s) of FIH1 according to the sequence alignment shown in Figure 2 A. The motivation to do so is

provided by the Hewitson et al. who disclose the need for "development of inhibitors selective for FIH versus the PHD isozymes or vice versa should be possible" (see right column, lines 22-24 on page 26355) to “provide s a further target for the development of therapeutic agents that augment HIF activity in ischemia/hypoxic disease” (see bottom of left column, page 26354). Accordingly, the invention taken as a whole is *prima facie* obvious.

13. Claims 1, 3, 5-6, 29 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewitson et al. (May 31, 2002, The Journal of Biological Chemistry, vol. 149, page 26351-26355) and Böhm (J. of Comp.-Aided Molec. Design, 1992, 6:61-78) and Goodsell et al. (J. of Molec. Recog., 1996, 9:1-5) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

The rejection was stated in the previous office action as it applied to previous Claims 3 and 30. In response to this rejection, applicants have cancelled Claims 2-3, 26 and 30; amended Claims 1, 4-6, 29 and 33; and traverse the rejection as it applies to the newly amended claims.

Applicants argue the instant rejection is moot in view of that Hewitson does not teach an assay as recited in the presently amended independent claims; and cancelling Claims 3 and 30.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. As noted above, Hewitson et al. also teach an FIH hydroxylase activity assay in the presence of N-oxaloylglycine in the FIH/HIF-1α CAD reaction step which inhibited the effect of FIH (see description of Figure 1 B, on page 26353). Also, the instant rejection applies to the newly amended claims as described below.

Hewitson et al. teach a method comprising comparing a structural model of phosphomannose isomerase (PMI) complexed with zinc, which are encompassed by the term FIH and a chemical entity, respectively, as shown in the three-dimensional structure in Figure 2-B, wherein the PMI three-dimensional structure meets the recited limitation of "structural model of said FIH is derived from structural factors or coordinates shown in Table 3" in Claim 1; wherein said FIH is any polypeptide comprising fragment or mutant of SEQ ID NO: 21; thus, meeting the limitation of Claim 1 because as noted above in the 112 2nd paragraph rejection, the limitation regarding the activity requirement has been deemed indefinite because *in silico* structures have no activity by virtue of being virtual images. The binding of Zn in the protein crystal structure of Hewitson et al. meets the limitations of Claim 4. Also addition to the 35 U.S.C 112, 2nd rejection above regarding the term "retains asparaginyl hydroxylase activity", the "identifying, screening, characterizing or designing a chemical entity which mimics or binds to FIH polypeptide comprising SEQ ID NO21 or a fragment or mutant thereof ... wherein the fragment or mutant retains asparaginyl hydroxylase activity" is a preamble reciting an intended use, which does not contribute any limitations to the

claimed method steps and given no patentable weight as an active method step. The Hewitson et al. reference recites zinc(II) inhibits FIH (see middle of right column, page 26353) and in view of the assay using HIF-1α-(775-826) as a substrate (see FIH Assays in bottom left column, page 26352), wherein the FIH of Hewitson et al. hydroxylate Asn803 of HIF (see title and bottom right column, page 26351); thus, the hydroxylation assay by Hewitson et al. using zinc meets the limitations of Claim 5. Thus, the method of Hewitson et al. anticipates Claims **1 and 4-5**.

Hewitson et al. do not teach in silico methods for identifying a chemical entity which binds to a FIH polypeptide comprising method step of utilizing the coordinates in Table 3.

Böhm teaches methods of rational drug design via computer modeling which either uses a library of known compounds as ligands, such as the Cambridge Structural Database, or the compounds can be designed de novo. In both scenarios, the protein structural coordinates of the protein of interest is input into the computer program and ultimately the computer software program does the rest in terms of identifying the best possible fit. Specifically, the program LUDI as designed by Böhm et al. teaches the de novo design of fragments or compounds which fit into the active site (see p. 61, abstract, p. 62, 2nd full paragraph and p. 64, Figure 1). Other programs exist, such as DOCK, which utilizes thousands of molecules that are located in the library of the Cambridge Structural Database in order to identify a molecule that fits spatially into the active site (these can be agonists, antagonists, inhibitors or modulators) (see p. 62, 1st full paragraph). The program AutoDock as taught by Goodsell et al. is a suite of three

different computer programs used to predict the bound conformations of small, flexible ligands to a macromolecular structure of known structure. The user simply inputs the structural coordinates and can choose either to design de novo potential ligands or to utilize a known library (see first paragraph of Introduction, p. 1). These descriptions are the instant methods and only lack the specific structural coordinates as disclosed in Table 1.

Thus, the only difference in the structure coordinate of Table 3 and the level of ordinary skill in the art for using any coordinate in the computer is rather simple, only if the coordinates are available. As noted in the previous Office action, this particular data required by the instant claims is considered to be nonfunctional descriptive material. In *Gulack* and *Ngai*, the respective Courts held that nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. According to *Gulack,* the key factor in analyzing the obviousness of the claims over the prior art is the determination that the machine-readable data comprising the structural coordinates of Table 3 is a known machine-readable medium and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. According to MPEP 2106.01, functional descriptive material consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of data structure is a physical or logical relationship among data elements, designed to support specific data

manipulation functions and that "Nonfunctional descriptive material" includes but is not limited to music, literary works, and a compilation or mere arrangement of data. In this case, the data of Table 3 is an arrangement of data that represents a 3-D molecular structure. The data of Table 3 is not a data structure or a computer program that imparts functionality when employed as a computer component. The Table 3 structural coordinates are regarded as non-functional descriptive material and the claimed method is the same as the method of Hewitson et al. The three-dimensional data of Table 3, which are processed using a series of processing steps using a known algorithm, do not appear to impose a change in the processing steps or functioning of the computer and there is no evidence of record that the data of Table 3 imposes a change in the function of the computer. Put another way, the function of the computer is the same whether the computer comprises the data of Table 3 or not. Thus, all claim limitations concerning the structure coordinate data of Table 3 are given no patentable weight as the data is considered to be non-functional descriptive material. See MPEP 2106 and the USPTO analysis of Cases 6-7 of the "Report on comparative study on protein three-dimensional structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" at www.trilateral.net/projects/biotechnology/protein_3d/.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the method as disclosed by Hewitson using any set of structural coordinates as defined in the claims with a reasonable expectation of success by the teachings of Hewitson et al., Bohm and Goodsell et al, in view of Gulack and Ngai. One would have been

motivated to do this because Hewitson discloses the biological and structural implication "provide s a further target for the development of therapeutic agents that augment HIF activity in ischemia/hypoxic disease" (see bottom of left column, page 26354) by "development of inhibitors selective for FIH versus the PHD isozymes or vice versa should be possible" (see right column, lines 22-24 on page 26355). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656